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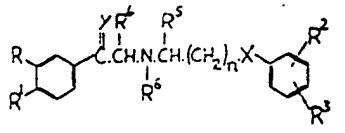
(54) SUBSTITUTED 1-PHENYL-2-ALKYLAMINO-ALKANOLS, 1-PHENYL-2-ALKYLAMINO-ALKANES AND α-AMINOALKYL PHENYL KETONES

(71) We, PFIZER LIMITED, a British Company, of Ramsgate Road, Sandwich, Kent, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The invention relates to alkanolamine, alkylamine and aminoalkyiketo derivatives having useful therapeutic properties. It is particularly concerned with novel substituted 1-phenyl-2-alkylaminoalkanols, 1 - phenyl - 2 - alkylamino-alkanes and α-aminoalkyl phenyl ketones which are β-agonists, i.e. stimulate the β-adrenergic receptors.

The compounds of the invention are those having the general formula:



(I)

where

R and R¹ each represent hydrogen or a hydroxy group, at least one being a hydroxyl group;

R² represents hydrogen, halogen or a lower alkyl or alkoxy group;

R³ represents an acylamino group, a lower alkoxycarbonylamino group, an amoyl group or a ureido group, as hereinafter defined, any one of which may be separated from the phenyl ring by a methylene or ethylene group;

R⁴, R⁵, and R⁶ each represent hydrogen or a lower alkyl group;

X represents oxygen, sulphur, imino or a direct link;

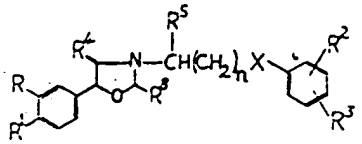
Y represents a hydrogen atom and a hydroxy group, two hydrogen atoms or an oxygen atom;

and

n is 1, 2 or 3 when X is other than a direct link and is 0 to 4 when X is a direct link; the carboxylic acid esters, and aldehyde condensation products, of such compounds; and their pharmaceutically-acceptable acid addition salts.

In this specification "halogen" comprises fluorine, chlorine, bromine and iodine; "imino" group indicates the group —NR⁷— where R⁷ represents hydrogen or a lower alkyl group; and the term "lower" used to qualify an alkyl or alkoxy group, indicates that such group contains up to 4 carbon atoms.

The aldehyde condensation products of the compounds of the invention are oxazolidones, having the formula:



(II)

which are formed by condensation of compounds of the invention in which R⁶ is hydrogen and Y represents a hydrogen atom and a hydroxy group with an aldehyde of the formula R⁸CHO, where R⁸ is hydrogen or a lower alkyl group.

The compounds of the invention have the property of stimulating the β-adrenergic recep-

[Price 25p]

tors. In particular, they increase the force of myocardial contraction, and are useful in the curative or prophylactic treatment of cardiac conditions such as congestive heart failure. By virtue of their β-receptor stimulating properties these compounds are also useful in the treatment of obstructive airways disease and peripheral vascular disease.

Particular embodiments of the invention comprise those compounds of the formula (I) wherein Y represents a hydrogen atom and a hydroxy group, two hydrogen atoms, or an oxygen atom, in any of which compounds R^1 represents a hydroxy group and R represents hydrogen, R and R^1 both represent a hydroxy group, or R represents a hydroxy group and R^1 represents hydrogen, and in any of which compounds R^2 is hydrogen.

In the above formulae, when R^3 is amoyl, it may be a carbamoyl or sulphamoyl group having the formula $—CO.NR^9R^{10}$ or $—SO_2.NR^9R^{10}$, respectively, where R^9 and R^{10} are each hydrogen or a lower alkyl or an aryl group or, together with the nitrogen atom to which they are attached, form a heterocyclic group, e.g. a pyrrolidino, piperidino, piperazino or morpholino group. When such a group is separated from the phenyl ring by a methylene or ethylene group, R^3 has the formula $—CH_2CONR^9R^{10}$, $—CH_2SO_2NR^9R^{10}$ $—CH_2CH_2CONR^9R^{10}$, or $—CH_2CH_2SO_2NR^9R^{10}$.

When R^3 is an acylamino group, it may be derived from the amide of a carboxylic or sulphonic acid, i.e. it may have the formula $R^{11}R^{12}N—$ where R^{11} is an acyl group derived from either a carboxylic or a sulphonic acid, R^{12} is hydrogen or a lower alkyl group, or R^{11} and R^{12} together with the nitrogen atom form a cyclic imido group. Moreover any such group may be separated from the phenyl ring by a methylene or ethylene group, in which case R^3 will have the formula $R^{11}R^{12}NCH_2—$ or $R^{11}R^{12}NCH_2CH_2—$.

Thus R^3 may be, for example, a formamido, acetamido, propionamido, acrylamido, cyclo-hexane carbonamido, benzamido, furamido, phenyl acetamido, methane sulphonamido, benzene sulphonamido group, or a substituted derivative thereof, e.g. a chloracetamido, trifluoroacetamido, glycolamido, phenoxyacetamido, toluamido, nitro-benzamido, chlorobenzamido or toluene sulphonamido group, or a corresponding amido-methyl or 2-amido-ethyl group, e.g. an acetamido-methyl or 2-acetamido-ethyl group. When $R^{11}R^{12}N—$ is a cyclic imido group, it may be derived from an aliphatic or aromatic dicarboxylic acid; thus R^3 may be, for example, a succinimido, maleimido or phthalimido group or a corresponding imidomethyl or 2-imido-ethyl group.

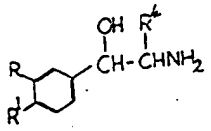
When R^3 is a ureido group, it may be ureido substituted with one or more lower alkyl groups on one or both of the nitrogen atoms. Thus it may be, for example, a 3-methyl ureido group. Furthermore, when R^3 is a lower alkoxycarbonylamino group, it may be, for example, an ethoxycarbonylamino group.

Acids from which pharmaceutically-acceptable addition salts of the compounds of the invention can be prepared are those which form non-toxic addition salts containing pharmaceutically-acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, saccharate and p-toluene sulphonate salts.

The compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route fo administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or colouring agents. They may be injected parenterally, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

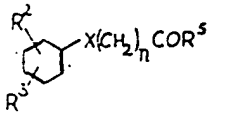
The compounds of the invention may be prepared in a number of ways:

(1) An amine of the formula:



(III)

is reacted with an aldehyde or ketone of the formula:

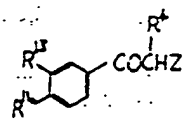


(IV)

to give the corresponding Schiff's base, which is reduced in the presence of a hydrogenation catalyst, e.g. platinum, to a compound of the invention in which R^6 is hydrogen and Y represents a hydrogen atom and a hydroxy group. After filtration and evaporation to dryness the product is isolated by trituration followed by crystallisation, or by dissolution in a suitable solvent and

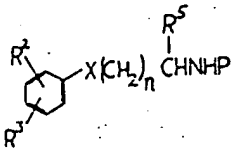
precipitation as a salt, e.g. the hydrochloride, maleate, fumarate or oxalate, by addition of the appropriate acid.

(2) A phenacyl halide of the formula:



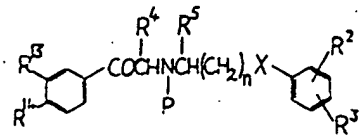
(V)

where Z is halogen and R^{13} and R^{14} each represent hydrogen or, a group PO—, where P is an easily hydrogenolysable protecting group, e.g. a benzyl group, at least one of R^{13} and R^{14} being a group PO—, is reacted with an amine of the formula:



(VI)

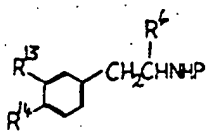
to give a compound of the formula:



(VII)

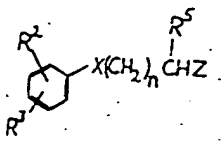
To obtain a compound of the invention in which Y represents a hydrogen atom and a hydroxy group and R^6 represents hydrogen, the ketonic compound is reduced to the corresponding secondary alcohol and the protecting groups (P) are removed by hydrogenolysis using a catalyst, e.g. palladium. To produce a compound of the invention in which Y represents an oxygen atom and R^6 represents hydrogen, the ketonic compound itself is freed of the protecting groups (P) by hydrogenolysis. The methods of isolation and purification are similar to those given for method (1).

(3) An amine of the formula:



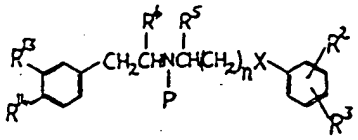
(VIII)

in which R^{13}, R^{14} and P are as defined in (2) above, is reacted with a halo-compound of the formula:



(IX)

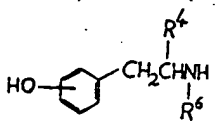
in which Z is halogen, to give a compound of the formula:



(X)

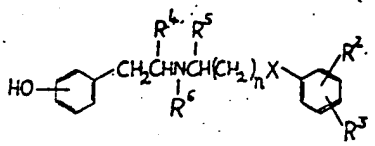
The protecting groups (P) are then removed by hydrogenolysis as before and the methods of isolation and purification are similar to those given for method (1).

(4) An amine of the formula:



(XI)

in which the single hydroxy group is in either the 3- or the 4- position, is reacted with a halo-compound of the formula (IX) to give a compound of the formula:

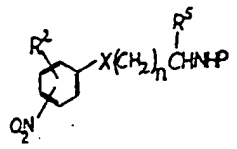


(XII)

The methods of isolation and purification are similar to those given for the method (1). Where R^6 is hydrogen, an excess amount of the amine is used to prevent excessive formation of the tertiary amine by-product.

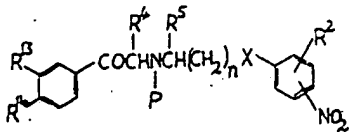
(5) The compounds of the invention in which R^3 represents an acylamino, a lower alkoxy carbonylamino or a ureido group

attached directly to the phenyl ring, i.e. groups wherein the free valency is on the nitrogen atom, R^6 represents a hydrogen atom, and Y represents a hydrogen atom and a hydroxy group or an oxygen atom, may be prepared from a phenacyl halide of the formula (V) as defined in method (2) and an amine of the formula:



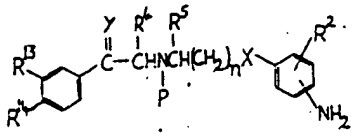
(XIII)

to give a compound of the formula:



(XIV)

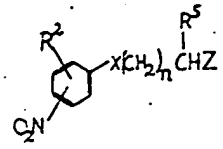
For the preparation of compounds wherein Y represents a hydrogen atom and a hydroxy group, the ketonic compound is then reduced to the corresponding secondary alcohol, whereas for the preparation of compounds wherein Y represents an oxygen atom, this stage is omitted. The nitro group is reduced by hydrogenation in the presence of a catalyst, e.g. Raney nickel, to an amino group to give a compound of the formula:



(XV)

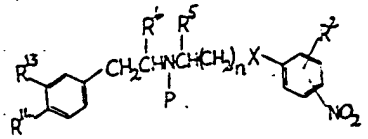
in which Y represents a hydrogen atom and a hydroxy group or an oxygen atom. The compound (XV) is then reacted with a suitable reagent for conversion of the amino group to an acylamino group, a lower alkoxycarbonylamino group or a ureido group; e.g. for conversion of the amino group to a formamido, ethoxycarbonylamino or a 3-methyl-ureido group, suitable reagents are formic acid, ethyl chloroformate and methyl*iso*cyanate respectively. Finally, the protecting groups (P) are removed by hydrogenolysis using a catalyst, e.g. palladium, to give a compound of the formula (I) wherein R^3 represents an acylamino, a lower alkoxycarbonylamino or a ureido group attached directly to the phenyl ring, and Y represents a hydrogen atom and a hydroxy group or an oxygen atom.

(6) The compounds of the invention in which R^3 represents an acylamino, a lower alkoxycarbonylamino or a ureido group attached directly to the phenyl ring, and Y represents two hydrogen atoms, may be prepared from an amine of the formula (VIII) as defined in method (3) and a halo-compound of the formula:



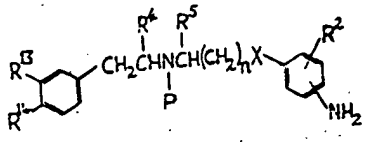
(XVI)

to give a compound of the formula:



(XVII)

The nitro group is then reduced by hydrogenation in the presence of a catalyst, e.g. Raney nickel, to an amino group to give a compound of the formula:



(XVIII)

The compound (XVIII) is then reacted with a suitable reagent for conversion of the amino group to an acylamino, a lower alkoxycarbonylamino or a ureido group such as are exemplified in method (5). Finally, the protecting groups (P) are removed by hydrogenolysis using a catalyst, e.g. palladium.

(7) The compounds of the invention in which R^6 represents a lower alkyl group may be prepared by the methods (2), (3), (5) and (6), but with the protecting groups (P) attached to the nitrogen atom in the starting materials (VI), (VIII), (XIII) and (XVIII) respectively, replaced by R^6.

(8) The aldehyde condensation products of the compounds of the invention may be prepared by reacting a compound of the invention in which R^4 and R^5 are each hydrogen with an aldehyde of the formula R^8CHO, where R^8 is hydrogen or a lower alkyl group, in a diluent or solvent, e.g. ethanol, preferably in the presence of an acid catalyst, e.g. hydrochloric or acetic acid, and preferably at an elevated temperature. The water formed in the reaction may be removed by azeotropic distillation by means of an entraining solvent, e.g. benzene, or by a dehydrating agent, e.g. anhydrous potassium carbonate.

In the general methods (5) to (8), the methods of isolation and purification are similar to those given for method (1).

The invention is illustrated by the following Examples.

Example 1

A mixture of DL-octopamine (4.6 g), 4-carbamoylphenoxy acetone (5.8 g) and ethanol (150 ml) was boiled under reflux for 8 hours in the presence of molecular sieves, then hydrogenated over platinum oxide at 50 p.s.i. and 50°C. Filtration and evaporation *in vacuo* of the filtrate gave a viscous oil which was triturated with ether to provide a semi-solid material. This material was then triturated with ethanol and the residual white solid crystallised from aqueous dimethylformamide to afford *DL - 2 - [2 - (4 - carbamoyl - phenoxy) - 1 - methyl - ethylamino] - 1 - (4-hydroxyphenyl) ethanol hemihydrate* (2.0 g), m.p. 195—198°C.

Analysis: —

Found:	C, 63.98;	H, 6.37;	N, 8.27%
Required for $C_{18}H_{22}N_2O_4.0.5H_2O$:	C, 63.70;	H, 6.83;	N, 8.26%

Example 2

Also prepared by the method described in Example 1 was DL-octopamine and 2-carbamoyl-4-methylphenoxy acetone was *DL-2-[2 - (2 - carbamoyl - 4 - methylphenoxy) - 1-methylethylamino] - 1 - (4 - hydroxyphenyl) ethanol*, isolated as the oxalate, m.p. 175—6°C.

Analysis: —

Found:	C, 58.23;	H, 6.43;	N, 6.65%
Required for $C_{19}H_{24}N_2O_4.C_2H_2O_4$:	C, 58.06;	H, 6.03;	N, 6.45%

Example 3

A stirred mixture of 4-benzyloxyphenacyl bromide (18.3), N-[2-(4-carbamoylmethylphenoxy)ethyl]benzylamine (17.0 g), anhydrous sodium carbonate (6.4 g) and ethanol (200 ml) was boiled under reflux for 1 hour, then allowed to cool and filtered. Evaporation *in vacuo* of the filtrate afforded an oil which could not be induced to solidify. It was thus stirred with a mixture of sodium borohydride (2.4 g), ethanol (100 ml) and 1,4-dioxan (100 ml) for 18 hours at room temperature. The resulting mixture was acidified with 50% aqueous acetic acid then evaporated *in vacuo* to provide an oil which on trituration with 10% aqueous sodium carbonate solution, gave a white powder (17.3 g). Crystallisation of a sample (2.0 g) from methanol furnished *DL - 2 - [N - benzyl - 2 - (4 - carbamoylmethylphenoxy)ethylamino] - 1 - (4-benzyloxyphenyl) ethanol hydrate* (0.9 g), m.p. 105—107°C.

Analysis: —

Found:	C, 72.99;	H, 6.86;	N, 5.31%
Required for $C_{32}H_{36}N_2O_5$:	C, 72.70;	H, 6.86;	N, 5.30%

The previous product (15.3 g) was hydrogenated over 10% palladium/charcoal (1.5 g) in 50% aqueous acetic acid solution (100 ml) in a Parr hydrogenator at 15 p.s.i. and room temperature. Filtration of the resulting mixture followed by evaporation *in vacuo* of the filtrate gave an oil which was neutralised by addition of 10% aqueous sodium carbonate solution. The aqueous phase was decanted and the residual oil treated with water in which it rapidly dissolved. On standing, the latter solution deposited a white solid; several more crops were obtained by concentration of this solution, and also from the decantate, to give a total yield of 6.9 g. Crystallisation from methanol afforded *DL - 2 - [2 - (4 - carbamoylmethylphenoxy)ethylamino] - 1 - (4 - hydroxyphenyl) ethanol* (4.1 g), m.p. 160—161°C.

Analysis: —

Found:	C, 65.85;	H, 6.72;	N, 8.36%
Required for $C_{18}H_{22}N_2O_4$:	C, 65.44;	H, 6.71;	N, 8.48%

Example 4

(A) A stirred mixture of 4-benzyloxyphenacyl bromide (15.25 g), N - [2 - (4 - sulphamoylphenoxy)ethyl]benzylamine (15.3 g), anhydrous sodium carbonate (5.3 g) and ethanol (200 ml), was

boiled under reflux for 1 hour, then allowed to cool, and filtered to remove the sediment of inorganic salts. Evaporation *in vacuo* of the filtrate afforded a yellow solid, which was distributed between water (500 ml) and chloroform (400 ml). The layers, which initially coalesced into an emulsion, were clarified by filtration through an anhydrous sodium carbonate pad. The chloroform layer was separated, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to afford a viscous yellow oil, which was found to be very impure from thin layer chromatography evidence. Addition of diethyl ether, chilling, evaporation of the solvent and standing at room temperature eventually solidified the oil to a cake, which was crushed, washed with diethyl ether and dried, providing a cream-coloured powder, yield 15.9 g, m.p. 110—115°C.

(B) A solution of the crude product of (A) (13.25 g) in 1:1 ethanol:1,4-dioxan (100 ml) was added over one minute to a stirred suspension of sodium borohydride (0.95 g) in ethanol (100 ml) at room temperature, and the mixture was stirred for a further 21 hours. The resulting mixture was then acidified with glacial acetic acid, the whole then being evaporated *in vacuo* to a tarry material to which was added aqueous sodium carbonate solution. Water was added, and the resulting solution extracted with chloroform. The layers, which initially coalesced into an emulsion, were clarified by filtrate through diatomaceous earth. The chloroform layer was separated, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to afford an oil which could not be induced to solidify despite trituration in 40—60°C. petrol ether and diethyl ether with chilling.

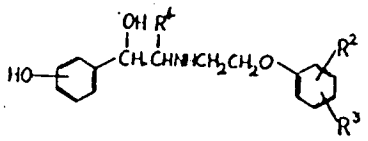
(C) The crude product of the previous stage (13.2 g) was hydrogenated over 10% palladium/charcoal (1.5 g) in glacial acetic acid (90 ml) in a Parr hydrogenator at 15 p.s.i. and room temperature. Filtration of the resulting mixture followed by evaporation *in vacuo* of the filtrate gave an oil which was dissolved in ethanol (200 ml). To the ethanolic solution was added concentrated hydrochloric acid which resulted in precipitation of a white crystalline solid, which, after concentration by evaporation of the suspension to a volume of 50 ml, was collected by filtration and dried. It was then dissolved in a boiling ethanol/methanol mixture, the solution filtered, and the filtrate chilled and diluted with diethyl ether. The resultant precipitate of white powder was collected by filtration and dried. The product, *DL-2-[2-(4-sulphamoylphenoxy)ethylamino]-1-(4-hydroxyphenyl) ethanol hydrochloride* (5.95 g) melted at 184°C. with decomposition.

Analysis:—

Found:	C, 49.33;	H, 5.58;	N, 7.14%
Required for $C_{16}H_{20}N_2O_5S.HCl$:	C, 49.42;	H, 5.44;	N, 7.21%

The following compounds have been prepared, using the method of Examples 3 and 4, from the appropriate starting materials.

The compounds of Examples 15, 16 and 17 were produced according to the method of Examples 3 and 4 but omitting the sodium borohydride reduction and effecting the hydrogenation of the carbonyl intermediate at a pressure of about 1000 p.s.i. and at room temperature in the presence of palladium/charcoal catalyst.



Example	R^2	R^3	R^4	Position of HO—	Salt/Free Base m.p. °C.	Analysis % (calculated in brackets) C	H	N
5	H	4—$CONH_2$	H	4—	Free base	64.56	6.27	8.86
					193—5°	(64.54	6.37	8.86)
6	H	4—$NHCOCH_3$	CH_3	4—	Hydrochloride	59.59	6.47	7.39
					213—6°*	(59.92	6.62	7.36)
7	H	4—$CONH_2$	CH_3	4—	Free base	65.41	6.63	8.25
					193—6°*	(65.44	6.71	8.48)
8	H	4—$NHCOCH_3$	H	3—	Hydrochloride sesquihydrate	54.56	6.01	7.25
					196—8°	54.89	6.64	7.11)
9	H	4—$NHCOCH_3$	H	4—	Hydrochloride	58.52	6.46	7.68
					211—2°	(58.92	6.32	7.64)

* three isomers

TABLE (Continued)

10	H	4—CH_2CONH_2	CH_3	4—	Free base	% C 66.34	% H 7.21	% N 7.88
					132—4° *	(66.26	7.02	8.13)
11	H	4—$NHCOCH_2CH_3$	H	4—	Hydrochloride	59.68	6.59	7.31
					192—3°	(59.90	6.61	7.35)
12	4—CH_3	2—$CONH_2$	H	4—	Hydrochloride	58.88	6.43	7.77
					160—2°	(58.94	6.32	7.64)
13	H	4—$NHSO_2CH_3$	H	4—	Free base	56.08	5.85	7.48
					151—3°	(55.72	6.05	7.64)
14	H	2—$NHCOCH_3$	H	4—	Acetate	61.77	6.61	7.14
					166—7°	(61.52	6.71	7.18)
15	H	4—$CONH_2$	CH_3	4—	Free base	65.58	6.74	8.28
					202—4° +	(65.44	6.71	8.48)
16	H	4—$NHCOCH_3$	CH_3	4—	Free base	66.43	7.03	8.01
					169—170° +	(66.26	7.02	8.13)
17	H	4—CH_2CONH_2	CH_3	4—	Free base	66.36	6.98	8.19
					162—4° +	(66.26	7.02	8.13)
18	H	4—$CH_2NHCOCH_3$	H	4—	Free base	66.13	7.06	7.84
					147.5—148.5°	(66.26	7.02	8.13)

*Three isomer
+erythro isomers

Example 19

A mixture of 3,4-dibenzyloxyphenacyl bromide (8.2 g), N - [2 - (4 - carbamoylphenoxy)ethyl]benzylamine (5.4 g), anhydrous sodium carbonate (2.1 g) and ethanol (250 ml) was boiled under reflux for 3 hours, then filtered hot to remove the inorganic sediment and cooled to 0°C. The resultant precipitated solid was collected by filtration, washed with diethyl ether and dried. The product, N-benzyl - N - (3,4 - dibenzyloxybenzoyl)-methyl - 2 - (4 - carbamoylphenoxy) ethylamine (11.0 g) melted at 140—2°C.

Analysis: —

Found:	C, 75.83;	H, 5.87;	N, 4.38%
Required for $C_{38}H_{38}N_2O_5.0.5H_2O$	C, 74.88;	H, 6.1;	N, 4.60%

Sodium borohydride (4.0 g) was dissolved in the minimum volume of water and 2 drops of 5N sodium hydroxide solution were added. The solution was added to a suspension of the previous product (10.5 g) in ethanol (300 ml) and the mixture stirred for 3 hours at room temperature, then gently warmed on a steam bath to achieve complete solution, and cooled again, stirring then being continued at room temperature for a further 36 hours. The solution was acidified by addition of a few drops of glacial acetic acid and the volume of the suspension reduced by one half. Water (300 ml) was added and the solid collected by filtration, washed in boiling water and dried to afford DL - 2 - [N - benzyl - 2 - (4-carbamoylphenoxy)ethylamino] - 1 - (3,4 - dibenzyloxyphenyl) ethanol (10.1 g), m.p. 110—1°C.

Analysis: —

Found:	C, 74.61;	H, 5.80;	N, 4.32%
Required for $C_{31}H_{32}N_2O_5.0.5H_2O$:	C, 74.60;	H, 6.43;	N, 4.58%

The previous product (6.0 g) was hydrogenated over 10% palladium/charcoal (600 mg) in 50% aqueous acetic acid solution (60 ml) in a Parr hydrogenator at 15 p.s.i. and room temperature. Filtration of the resulting mixture followed by evaporation *in vacuo* of the filtrate at less than 40°C. gave a brown syrup. Addition of an *iso*propanol/methanol mixture gave a solution and a black solid. The latter was removed by filtration and to the filtrate was added ethereal hydrogen chloride, which produced a gum. Decantation followed by trituration of the gum in methanol afforded a pink solid A (0.4 g). The decanted *iso*propanol/methanol/diethyl ether solution was concentrated by evaporation *in vacuo*, which resulted in precipitation of some more pink solid B (1.3 g). The filtrates from the collections of solids A and B were combined and treated with a small volume of diethyl ether. Cooling of this solution at 0°C. produced a third crop of crystals, solid C (0.2 g). Solids A, B and C, were combined and dissolved in the minimum volume of methanol, to which was added an approximately equal volume of *iso*propanol. The solution was concentrated by evaporation until such time as formation of crystals was first observed, after which the solution was cooled at 0°C. during which time more crystallisation occurred. The product, collected by filtration and dried, consisted of *DL - 2 - [2 - (4 - carbamoylphenoxy)ethylamino] - 1 - (3,4 - dihydroxyphenyl) ethanol hydrochloride* (1.05 g), m.p. 184°C. with decomposition.

Analysis: —

Found:	C, 54.98;	H, 5.87;	N, 7.34%
Required for $C_{17}H_{20}N_2O_5.HCl$:	C, 55.36;	H, 5.74;	N, 7.60%

Example 20

A mixture of 3,4 - dibenzyloxyphenacyl bromide (32.8 g), N - [2 - (4 - acetamidophenoxy)ethyl]benzylamine (22.8 g), anhydrous sodium carbonate (8.4 g) and ethanol (1 litre) was boiled under reflux for 2 hours, then filtered hot to remove the inorganic sediment and evaporated *in vacuo* to afford a thick syrup. The latter was dissolved in hot *iso*propanol and the solution cooled, the precipitated solid then being collected by filtration. To a hot solution of the solid in fresh *iso*propanol were added a few millilitres of ethyl acetate, and the solution was then allowed to cool to room temperature. The crystallised solid was collected by filtration, washed in diethyl ether and dried. Recrystallisation from an *iso*propanol/ethyl acetate mixture afforded N-benzyl - N - (3,4 - dibenzyloxybenzoyl)-N - benzyl - N - (3,4 - dibenzyloxybenzoyl)-methyl - 2 - (4 - acetamidophenoxy) ethylamine (32.8 g), m.p. 104—6°C.

Analysis: —

Found:	C, 75.93;	H, 6.28;	N, 4.13%
Required for $C_{31}H_{30}N_2O_5$:	C, 76.20;	H, 6.23;	N, 4.56%

Sodium borohydride (12.0 g) was dissolved in water (40 ml) and 8 drops of 5N sodium hydroxide solution were added. The solution was added to a suspension of the previous product (32.8 g) in ethanol (800 ml) and the mixture gently warmed on a steam bath to achieve

complete solution. After removal of the steam bath, the solution was stirred for 10 minutes and poured into water containing a little acetic acid, which resulted in the precipitation of a gummy solid. The latter was extracted into chloroform and the chloroform solution separated and evaporated down *in vacuo* to give a syrup (20.4 g), which consisted of crude DL-2-[N - benzyl - 2 - (4 - acetamidophenoxy)ethylamino]-1-(3,4-dibenzyloxyphenyl) ethanol.

The previous product (20.0 g) was hydrogenated over 10% palladium/charcoal (2.0 g) in 50% aqueous acetic acid solution (200 ml) in a Parr hydrogenator at 15 p.s.i. and room temperature. Filtration of the resulting mixture followed by evaporation *in vacuo* of the filtrate at less than 40°C. gave a syrup, which was subsequently taken up into toluene and the solution evaporated down, this process being repeated until the residue consisted of a pink solid. The latter was dissolved in hot methanol and *iso*propanol added to the solution. After removal of excess methanol by evaporation *in vacuo*, a precipitate formed, and this was collected by filtration and dried (yield 11.2 g; m.p. 150°C. with decomposition). Recrystallisation from ethanol afforded 7.1 g of crystalline material, m.p. 165°C. with decomposition. The filtrate from the crystallisation in *iso*propanol/methanol was treated with ethereal hydrogen chloride, which resulted in precipitation of white crystals (4.6 g) of *DL-2 - [2 - (4 - acetamidophenoxy)ethylamino]-1-(3,4-dihydroxyphenyl) ethanol hydrochloride hemihydrate*, m.p. 176°C. with decomposition.

Analysis: —

Found:	C, 55.27;	H, 6.21;	N, 6.88%
Required for $C_{18}H_{22}N_2O_5.HCl.0.5H_2O$:	C, 55.16;	H, 5.92;	N, 7.15%

Example 21

Also prepared by the method described in Examples 19 and 20 from 3,4 - dibenzyloxyphenacyl bromide and N - [2 - (4 - carbamoylmethylphenoxy)ethyl]benzylamine was DL-2-[2 - (4 - carbamoylmethylphenoxy)ethylamino] - 1 - (3,4 - dihydroxyphenyl) ethanol hydrochloride, m.p. 224—8°C.

Analysis: —

Found:	C, 56.49;	H, 6.04;	N, 7.51%
Required for $C_{16}H_{22}N_2O_5.HCl$:	C, 56.47;	H, 6.05;	N, 7.32%

Example 22

A mixture of 3,4-dibenzyloxyphenacyl bromide (32.8 g), N - [2 - (4 - carbamoylmethylphenoxy)ethyl]benzylamine (22.8 g), anhydrous sodium carbonate (8.4 g) and ethanol (1 litre) was boiled under reflux for 3 hours, then filtered hot to remove the inorganic sediment and evaporated *in vacuo* to afford a thick syrup. The latter was crystallised upon trituration in diethyl ether and a sample of the resultant solid was recrystallised from ethanol to give N - benzyl - N - (3,4 - dibenzyloxybenzoyl))methyl - 2 - (4 - carbamoylmethylphenoxy) ethylamine, m.p. 99—101°C.

Analysis: —

Found:	C, 75.42;	H, 6.22;	N, 4.17%
Required for $C_{30}H_{30}N_2O_5.0.5H_2O$:	C, 75.10;	H, 6.30;	N, 4.49%

The previous product (7.0 g) was hydrogenated over 10% palladium/charcoal (700 mg) in 50% aqueous acetic acid solution (70 ml) in a Parr hydrogenator at 15 p.s.i. and room temperature. Filtration of the resulting mixture was followed by evaporation *in vacuo* of the filtrate to dryness, the crude product then being azeotroped in turn with water and toluene. The resulting syrup was dissolved in methanol, and ethereal hydrogen chloride was slowly added to the methanolic solution, yielding a precipitate of fawn crystals (4.0 g) which were subsequently collected by filtration and recrystallised from water with a little concentrated hydrochloric acid added. The crystals were collected by filtration and dried to give *2 - (4 - carbamoylethyl - phenoxy) - N - (3,4-dihydroxybenzoyl)methylethylamine hydrochloride* (3.0 g), m.p. 240°C. with decomposition.

Analysis: —

Found:	C, 57.01;	H, 5.73;	N, 7.22%
Required for $C_{18}H_{20}N_2O_5.HCl$:	C, 56.78;	H, 5.55;	N, 7.36%.

Example 23

Also prepared by the method described in Example 22 from 3,4-dibenzyloxyphenacyl bromide and N-[2-(2-carbamoyl-4-methylphenoxy)ethyl]benzylamine was *2 - (2 - carbamoyl - 4 - methylphenoxy) - N - (3,4 - dihydroxybenzoyl)methyl ethylamine hydrochloride hemihydrate*, m.p. 180°C., with decomposition between 218—223°C.

Analysis:—

Found:	C, 55.62;	H, 5.62;	N, 7.37%
Required for $C_{18}H_{20}N_2O_5.HCl.0.5H_2O$:	C, 55.44;	H, 5.69;	N, 7.19%

Example 24

A mixture of N-2-(3,4-dibenzyloxyphenyl)-ethyl benzylamine (13.6 g), 2-(4-sulphamoyl-phenoxy)ethyl chloride (4.8 g) and dry xylene (50 ml) was boiled under reflux for 12 hours. The solution was cooled and the precipitated solid removed by filtration, the filtrate then being evaporated *in vacuo* to dryness and taken up into diethyl ether. Insoluble material was removed from the ethereal solution by filtration, and the filtrate treated with ethereal hydrogen chloride, which resulted in the precipitation of a yellow solid. The latter was collected by filtration and recrystallised from a methanol/*iso*propanol mixture, giving N-[2-(3,4 - dibenzyloxyphenyl)ethyl] - N - [2-(4 - sulphamoylphenoxy)ethyl]benzylamine hydrochloride (5.8 g), m.p. 178—181°C.

Analysis:—

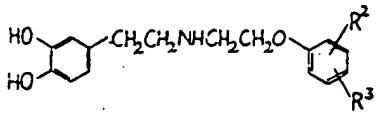
Found:	C, 67.62;	H, 6.03;	N, 4.26%
Required for $C_{37}H_{36}N_2O_5S.HCl$:	C, 67.40;	H, 5.96;	N, 4.25%

The previous product (5.7 g) was hydrogenated over 10% palladium/charcoal in glacial acetic acid in a Parr hydrogenator at 15 p.s.i. and room temperature The catalyst was removed by filtration and the filtrate evaporated *in vacuo* to a gum, which was triturated in a little acetone. The resulting grey solid was filtered off, and recrystallised from 5N hydrochloric acid giving *N-[2-(3,4-dihydroxyphenyl)ethyl] - 2 - (4 - sulphamoyl-phenoxy) ethylamine hydrochloride* as pale mauve crystals, m.p. 245—7°C.

Analysis:—

Found:	C, 49.39;	H, 5.41;	N, 7.31%
Required for $C_{16}H_{20}N_2O_5S.HCl$:	C, 49.40;	H, 5.44;	N, 7.20%

The following compounds have been prepared, using the method of Example 24, from the appropriate starting materials.



Example	R^2	R^3	Salt m.p. °C.	Analysis % (calculated in brackets) C	H	N
25	4—CH_3	2—$CONH_2$	Hydrochloride 200—202°	58.66 (58.93	6.33 6.32	7.47 7.64)
26	H	4—$CONH_2$	Hydrochloride 241—3°	57.46 (57.87	5.90 5.71	8.02 7.94)

Example 27

A mixture of N - 2 - (3,4 - dibenzyloxy-phenyl)ethyl benzylamine (12.0 g), 2-(4-acetamidophenoxy)ethyl chloride (3.1 g) and dry dimethylformamide (10 ml) was boiled under reflux for 10 hours. The solution was cooled, more dimethylformamide (15 ml) added, and the precipitated solid removed by filtration. The filtrate was evaporated *in vacuo* to dryness and the resultant solid stirred in chloroform, after which undissolved material was removed by filtration and the filtrate was evaporated *in vacuo* to dryness to give the crude product, N - [2 - (3,4 - dibenzyloxyphenyl)-ethyl] - N - [2 - (4 - acetamidophenoxy)-ethyl]benzylamine.

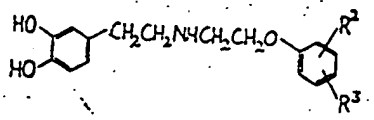
The previous product was hydrogenated over 10% palladium/charcoal in aqueous acetic acid with a few drops of concentrated hydrochloric acid added in a Parr hydro-

genator at 15 p.s.i. and room temperature. The catalyst was removed by filtration and the filtrate evaporated *in vacuo* to a gummy solid. The latter was crystallised from dilute hydrochloric acid, giving *N - [2 - (3,4 - dihydroxyphenyl)ethyl] - 2 - (4 - acetamidophenoxy)ethylamine hydrochloride* (2.5 g), m.p. 219—221°C.

Analysis: —

Found:	C, 58.97;	H, 6.26;	N, 7.90%
Required for $C_{18}H_{22}N_2O_4.HCl$:	C, 58.93;	H, 6.32;	N, 7.64%

The following compounds have been prepared, using the method of Example 27, from the appropriate starting materials.



Example	R^2	R^3	Salt m.p. °C.	Analysis % (calculated in brackets) C	H	N
28	2—OCH_3	4—$CONH_2$	Hydrochloride 0.25 hydrate	55.80	6.22	7.09
			168—171°	(55.82	6.05	7.23)
29	H	3—$CONH_2$	Hydrochloride	57.97	5.92	7.79
			211—4°	(57.87	5.71	7.94)
30	H	4—CH_2CONH_2	Hydrochloride 219—221°	58.83 (58.93	6.35 6.32	7.45 7.64)

Example 31

A mixture of 2 - (4 - hydroxyphenyl)ethylamine (5.6 g), 2 - (4 - carbamoylphenoxy)ethyl chloride (4.0 g) and dimethylformamide (25 ml) was heated at 140°C. for 4 hours. After cooling to room temperature, the mixture was poured into water and the resultant precipitated solid was collected by filtration, washed in turn with water, acetone and diethyl ether, and finally dried. The product, *N - [2 - (4 - hydroxyphenyl)ethyl] - 2 - (4-carbamoylphenoxy)ethylamine hydrochloride* melted with decomposition at 284°C.

Analysis: —

Found:	C, 60.41;	H, 6.33;	N, 8.56%
Required for $C_{17}H_{20}N_2O_3.HCl$:	C, 60.62;	H, 6.28;	N, 8.32%

Example 32

Also prepared by the method described in Example 31 from 2-(4-hydroxyphenylethylamine and 2 - (4 - acetamidophenoxy)ethyl chloride was *N - [2 - (4 - hydroxyphenyl)-ethyl] - 2 - (4 - acetamidophenoxy)ethylamine hydrochloride*, m.p. 275—7°C.

Analysis: —

Found:	C, 61.51;	H, 6.64;	N, 8.01%
Required for $C_{18}H_{22}N_2O_3.HCl$:	C, 61.62;	H, 6.61;	N, 7.99%

Example 33

(A) A stirred suspension of 4-benzyloxyphenacyl bromide (30.5 g), N-benzyl-2-(4 - nitrophenoxy)ethylamine hydrochloride (30.85 g) and anhydrous sodium carbonate (21.2 g) in ethanol (300 ml) was boiled under reflux for 1½ hours. The mixture was then filtered while still hot to remove sodium salts and the ethanolic filtrate evaporated *in vacuo* to a brown oil (48.7 g), consisting of crude N-benzyl-N - (4 - benzyloxybenzoyl)methyl - 2-(4-nitrophenoxy)ethylamine.

(B) Addition of 1,4-dioxan (150 ml) to the product of (A) caused precipitation of some white solid. The latter was removed

by filtration, and the dark brown filtrate added over 5 minutes to a stirred suspension of sodium borohydride (3.8 g) in ethanol (100 ml) at room temperature. Stirring was continued for 20 hours, after which the mixture was acidified with glacial acetic acid, diluted by addition of water and basified with aqueous sodium carbonate solution. The solution was extracted with chloroform (2×200 ml) and the chloroform solutions separated, combined, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to a brown oil (41.8 g), consisting of crude DL - 2 - [N - benzyl - 2 - (4-nitrophenoxy)ethylamino] - 1 - (4 - benzyloxyphenyl) ethanol.

(C) The crude product of (B), dissolved in a mixture of ethanol (150 ml) and 1,4-dioxan (50 ml), was submitted to hydrogenation at 50 p.s.i. and room temperature in the presence of Raney nickel catalyst. Removal of catalyst by filtration followed by evaporation of the filtrate *in vacuo* yielded crude DL - 2 - [N - benzyl - 2 - (4 - aminophenoxy)ethylamino] - 1 - (4 - benzyloxyphenyl) ethanol (37.85 g) as a dark brown tar.

(D) A solution of methyl *iso*cyanate (2.85 g) in chloroform (25 ml) was added over ½ minute to a stirred solution of the product of (C) (23.4 g) in chloroform (100 ml). Stirring at room temperature was continued for 2½ hours, after which the solution was evaporated *in vacuo* to a brown oil. A small sample of the latter yielded a white powder on trituration in 40—60° petrol ether/diethyl ether/acetonitrile, and the remaining oil was triturated in 40—60° petrol ether, the mixture being seeded with the foregoing white powder to yield, on standing, a grey solid mass. The latter was crushed and dried, and consisted of crude DL-2-[N - benzyl - 2 - (4 - {3 - methylureido}phenoxy)ethylamino] - 1 - (4-benzyloxyphenyl) ethanol. A small portion was crystallised from acetonitrile to yield crystals, m.p. 113—116°C.

Analysis: —

Found:	C, 72.82;	H, 6.59;	N, 8.01
Required for $C_{32}H_{38}N_3O_4$:	C, 73.12;	H, 6.71;	N, 8.00

(E) The product of (D) (22.0 g) dissolved in glacial acetic acid was hydrogenated at 15 p.s.i. and room temperature in the presence of palladium/charcoal catalyst. The catalyst was then removed by filtration and the filtrate treated with concentrated hydrochloric acid (4 ml, ~1 equivalent) and evaporated *in vacuo* to a green oil, which was triturated in diethyl ether/*iso*propanol to afford a grey tar. Trituration of the latter in acetonitrile (100 ml) yielded an off-white powder (12.75 g), which was subsequently dissolved in the minimum amount of warm water, the solution then being basified with aqueous sodium carbonate solution. The aqueous phase was decanted from the precipitated green tar and the latter triturated in turn in diethyl ether and acetone. Successive triturations in fresh amounts of acetonitrile induced solidification to give a cream-coloured product (8.45 g). Crystallisation from ethanol/water afforded a cream-coloured solid, m.p. 155—160°C. with decomposition. A silver nitrate test on the product indicated the presence of halide and so it was inferred that the product was contaminated with the hydrochloride salt. The aqueous ethanol filtrate was evaporated *in vacuo* to dryness and the residue combined with the crystallised solid, m.p. 155—160°C., and the whole treated with warm aqueous saturated sodium carbonate solution to convert it to the free base. Resulting was a fawn powder (6.0 g) which was crystallised from ethanol to provide fawn crystals (3.7 g), m.p. 164—166°C. with decomposition. A final recrystallisation from an ethanol/methanol mixture yielded light fawn crystals (2.85 g) of *DL - 1 - (4 - hydroxyphenyl) - 2 - [2-(4 - {3 - methylureido}phenoxy)ethylamino]* ethanol, m.p. 165—6°C. with decomposition.

Analysis: —

Found:	C, 62.86;	H, 6.80;	N, 11.88%
Required for $C_{18}H_{23}N_3O_4$:	C, 62.59;	H, 6.71;	N, 12.17%

Example 34

Ethyl chloroformate (5.45 g) was added dropwise over 2—3 minutes to a stirred, warm suspension of DL - 2 - [N - benzyl - 2 - (4-aminophenoxy)ethylamino] - 1 - (4 - benzyloxyphenyl) ethanol (23.4 g) (prepared as described in Example 33 (A), (B) and (C) and anhydrous potassium carbonate (6.9 g) in ethanol (150 ml) and the stirred mixture was boiled under reflux for ½ hour. The suspension was then filtered hot to remove off-white solid and the filtrate evaporated *in vacuo* to a brown tar (27.0 g), consisting of crude DL-2 - [N - benzyl - 2 - (4 - ethoxycarbonylaminophenoxy)ethylamino] - 1 - (4 - benzyloxyphenyl) ethanol hydrochloride.

The previous crude product (27.0 g) was dissolved in 1:1 glacial acetic acid: water (240 ml) and hydrogenated at 15 p.s.i. and room temperature over 10% palladium/charcoal catalyst. The catalyst and some accompanying grey solid (independently shown to consist in all probability of the mono-O-benzyl compound mainly) were filtered off, and the yellow aqueous acetic acid filtrate evaporated *in vacuo* at 40°C. to give a fawn gum, which was triturated in diethyl ether (2×250 ml), the resultant fawn solid then being collected by filtration, dried at 80°C. *in vacuo* and crystallised from ethanol. The product consisted of off-white crystals (2.25 g) of *DL - 2 - [2 - (4 - ethoxycarbonylaminophenoxy)ethylamino] - 1 - (4 - hydroxyphenyl)ethanol hydrochloride*, which melted with decomposition in the range 187—9°C. to an opaque melt, the latter decomposing further with clarification in the range 225—230°C.

Analysis: —

Found:	C, 57.64; H, 6.06; N, 6.94%
Required for $C_{19}H_{24}N_2O_5.HCl$:	C, 57.49; H, 6.35; N, 7.06%

Example 35

90% Aqueous formic acid solution (4.3 ml) was added dropwise over 2—3 minutes to a stirred, warm solution of DL-2-[N-benzyl-2-(4 - aminophenoxy)ethylamino] - 1 - (4-benzyloxyphenyl) ethanol (23.4 g) (prepared as described in Example 33 (A), (B) and (C)) in benzene (150 ml), and the stirred solution was boiled under reflux for 1 hour. Evaporation of the solution, which consisted of two liquid layers, *in vacuo* afforded a brown oil, and this was then diluted with water (200 ml) and the pH adjusted to about 6.5 using saturated aqueous sodium carbonate solution. The solution extracted with chloroform (2×100 ml), the chloroform layers then being separated, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to afford a brown tar (26.0 g), which consisted of crude DL - 2 - [N - benzyl - 2 - (4 - formamidophenoxy)ethylamino] - 1 - (4 - benzyloxyphenyl) ethanol.

The previous crude product (26.0) was dissolved in glacial acetic acid (120 ml) and hydrogenated at 15 p.s.i. and room temperature over 5% palladium/charcoal catalyst. Evaporation of the filtrate *in vacuo* at 40°C. from the removal of catalyst yielded a brown tar, which was azeotroped with benzene (2×100 ml). To the resulting brown tar was added water (150 ml), and the pH of the solution containing suspended white solid, was adjusted from about 4.5 to about 9.5, at which point the solution contained a fawn precipitate. The residual tar was converted to solid by stirring, the whole solid then being collected by filtration and recrystallised twice from ethanol to give fawn crystals (6.55 g) of DL-1-(4-benzyloxyphenyl) - 2 - [2 - (4 - formamidophenoxy)-ethylamino] ethanol, m.p. 151.5—152.5°C.

Analysis: —

Found:	C, 70.56; H, 6.45; N, 6.27%
Required for $C_{24}H_{24}N_2O_4$:	C, 70.91; H, 6.45; N, 6.89%

The previous product (4.06 g) was dissolved in glacial acetic acid (60 ml) and hydrogenated at 15 p.s.i. and room temperature over 10% palladium/charcoal catalyst. Removal of the catalyst by filtration, followed by evaporation *in vacuo* of the filtrate afforded a brown oil, to which was added saturated aqueous sodium carbonate solution. The resultant gum was solidfied by trituration in ethanol, and the solid collected by filtration and crystallised from ethanol to yield off-white crystals (2.3 g) of *DL - 2 - [2 - (4 - formamidophenoxy)ethylamino] - 1 - (4 - hydroxyphenyl) ethanol*, m.p. 164—5°C. with decomposition, which was found from nuclear magnetic resonance spectroscopy to contain about 10% ethanol.

Analysis: —

Found:	C, 64.69; H, 6.52; N, 8.92%
Required for $C_{17}H_{20}N_2O_4.0.1C_2H_5OH$:	C, 64.37; H, 6.47; N, 8.73%

Those compounds of the invention in which Y represents a hydrogen atom and a hydroxy group exist in D- and L- optically active isomeric forms and the invention includes these forms as well as the racemic mixtures. Method (1) described above may be used to prepare the optically active isomers by using the appropriately substituted phenyl-ethanolamine enantiomer as starting material, whereas methods (2) and (5) applied to such compounds of the invention will result in the production of a racemic mixture. Alternatively, the racemic product of each of the above methods may be resolved by well-known techniques, e.g. by fractional crystallisation of an addition salt formed with an optically active acid.

Compounds in which R^4 and/or R^5 are other than hydrogen have more than one asymmetric centre and exist as two or more racemic pairs of diastereoisomers. In general, the products of the above methods will be a

mixture of the pairs of stereoisomers, and these pairs may usually be separated from each other by physical methods, e.g. by fractional crystallisation or chromatography of the free bases or suitable salts. The invention includes the separated pairs, as well as mixtures thereof, as racemic mixtures or as separated D- and L- forms.

The activity of compounds of the invention as β-adrenergic stimulants for the heart has been shown by their effectiveness in one or more of the following tests: (a) increasing the force of contraction of the isolated electrically driven guinea-pig left atrium, and of isolated electrically driven cat papillary muscle; (b) increasing the force and/or rate of contraction of spontaneously beating guinea-pig atria; (c) increasing cardiac output in the anaesthetised cat with an implanted left ventricular catheter; (d) increasing cardiac output in the conscious dog with an implanted left ventricular catheter.

In test (a), the increased contractility of the muscle in response to the test compound is measured in two animal species (guinea-pig and cat). The experiments are then repeated in the presence of a β-receptor blocking agent and on reserpinised atria to determine whether the test compound is a directly acting β-receptor agonist.

In test (b) any selective action of compounds of the invention is shown compared with the catecholamines, noradrenaline and adrenaline, i.e. whether or not they increase the force of atrial contraction to a greater extent than the rate.

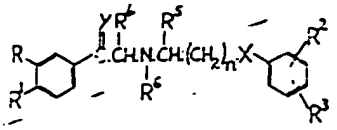
In test (c) the inotropic action of the test compounds following intravenous administration is measured in the anaesthetised cat. The peripheral effects of the compounds (e.g. effect on blood pressure) are also measured in this preparation.

In test (d) the inotropic action of the test compound following oral administration to a dog with an implanted left ventricular catheter is measured.

By virtue of their performance in tests (a) to (d), the preferred compounds are to be found generally in those compounds of the invention in which R represents hydrogen, R^1 represents a hydroxy group, R^6 represents hydrogen, X represents oxygen, Y represents a hydrogen atom and a hydroxy atom, and n is 1. More particularly, the preferred compounds have the above features and in addition R^1 and R^3 each represent hydrogen. Particularly preferred compounds are those which show good potency of activity in test (a), and which show a good inotropic response and good duration of action accompanied by only a slight increase in heart rate in test (c), and are specifically DL - 2 - [2 - (4 - carbamoylphenoxy)ethylamino] - 1 - (4 - hydroxyphenyl) ethanol, DL - 1 - (4 - hydroxyphenyl) - 2 - [2 - (4 - (3 - methylureido)-phenoxy)ethylamino] ethanol and DL - 2-[2 - (4 - formamidophenoxy)ethylamino] - 1-(4 - hydroxyphenyl) ethanol. Two more compounds, DL - 2 - [2 - (4 - carbamoylmethylphenoxy)ethylamino] - 1 - (4 - hydroxyphenyl) ethanol and DL - 2 - [2 - (4 - acetamidophenoxy)ethylamino] - 1 - (4 - hydroxyphenyl) ethanol hydrochloride show good potency of activity in test (a), but are inferior to the three particularly preferred compounds in test (c).

WHAT WE CLAIM IS:—

1. Compounds having the formula:



where

R and R^1 each represent hydrogen or a hydroxy group, at least one being a hydroxy group;

R^2 represents hydrogen, halogen or a lower alkyl or alkoxy group;

R^3 represents an acylamino group, a lower alkoxycarbonylamino group, an amoyl group or a ureido group, as hereinbefore defined, any one of which may be separated from the phenyl ring by a methylene or ethylene group;

R^4, R^5, and R^6 each represent hydrogen or a lower alkyl group;

X represents oxygen, sulphur, imino or a direct link;

Y represents a hydrogen atom and a hydroxy group, two hydrogen atoms or an oxygen atom;

and

n is 1, 2 or 3 when X is other than a direct link and is 0 to 4 when X is a direct link; the carboxylic acid esters, and aldehyde condensation products, of such compounds, as hereinbefore defined; and their pharmaceutically-acceptable acid addition salts.

2. Compounds as claimed in Claim 1, in which X represents oxygen and n is 1.

3. Compounds as claimed in Claim 1 or Claim 2, in which Y represents a hydrogen atom and a hydroxy group.

4. Compounds as claimed in Claim 1 or Claim 2, in which Y represents two hydrogen atoms.

5. Compounds as claimed in Claim 1 or Claim 2, in which Y represents an oxygen atom.

6. Compounds as claimed in any preceding claim, in which R^6 represents a hydrogen atom.

7. Compounds as claimed in any preceding claim, in which R^3 represents a hydrogen atom.

8. Compounds as claimed in any preceding

claim, in which R^4 represents a hydrogen atom.

9. Compounds as claimed in any preceding claim, in which R^1 represents a hydroxy group and R represents hydrogen.

10. Compounds as claimed in any of Claims 1—8, in which R and R^1 both represent a hydroxy group.

11. Compounds as claimed in any of Claims 1—8, in which R represents a hydroxy group and R^1 represents hydrogen.

12. Compounds as claimed in any preceding claims, in which R^3 represents a carbamoyl, acetamido, formamido, propionamido, sulphamoyl, 3-methylureido, ethoxycarbonylamino or a methane sulphonamido group, optionally separated from the phenyl ring by a methylene or an ethylene group.

13. Compounds as claimed in any preceding claim, in which R^2 represents hydrogen.

14. DL - 2 - [2 - (4 - carbamoylphenoxy)-ethylamino] - 1 - (4 - hydroxyphenyl) ethanol and its pharmaceutically-acceptable acid addition salts.

15. DL - 1 - (4 - hydroxyphenyl) - 2-[2 - (4 - {3 - methylureido}phenoxy)ethylamino] ethanol and its pharmaceutically-acceptable acid addition salts.

16. DL - 2 - [2 - (4 - formamidophenoxy)-ethylamino] - 1 - (4 - hydroxyphenyl) ethanol and its pharmaceutically-acceptable acid addition salts.

17. DL - 2 - [2 - (4 - carbamoylmethyl-phenoxy)ethylamino] - 1 - (4 - hydroxy-phenyl) ethanol and its pharmaceutically-acceptable acid addition salts.

18. DL - 2 - [2 - (4 - acetamidophenoxy)-ethylamino] - 1 - (4 - hydroxyphenyl) ethanol and its pharmaceutically-acceptable acid addition salts.

19. A compound as claimed in Claim 1 the preparation of which is described in any one of the Examples.

20. A pharmaceutical composition comprising a compound as claimed in any preceding claim and a pharmaceutically-acceptable carrier material.

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